REMARKS

Claims 1, 3, 5, 7-15, and 28-39 are pending in the application. Claims 28-39 are withdrawn from consideration. Applicants propose to amend claims 1, 3, 5, and 7. Support for the amendment to claims 1, 3, 5, and 7 can be found in the specification, e.g., at page 8, lines 8-10. Applicants have also amended those claims to remove the phrase "the group consisting of."

Applicants submit that the proposed amendments do not raise new issues or necessitate the undertaking of any additional search of the art by the Examiner. Those amendments also place the application in better condition for allowance or appeal. Thus, entry of the amendment is respectfully requested.

Rejections under 35 U.S.C. § 112, first paragraph

The Examiner rejected claims 1, 3, 5, and 7-15 under 35 U.S.C. § 112, first paragraph, as allegedly "containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention." Action at page 2. Specifically, the Examiner alleged that "other undescribed molecules such as antibodies, agonists and antagonists of the receptor are also capable of binding to the receptor. Therefore, this description of the nucleic acid by the binding function of the protein it encodes does not fulfill the requirements of 35 USC 112, first paragraph, written description." Action at page 3.

Applicants respectfully traverse. Solely to expedite prosecution and without acquiescing to the rejection, applicants propose to amend claims 1, 3, 5, and 7 as follows:

> 1. An isolated nucleic acid encoding a hek-L protein capable of binding hek and affecting the growth and differentiation of cells expressing hek, wherein said nucleic acid comprises a nucleotide sequence that is at least 90% identical to a sequence selected from nucleotides 83-796, 83-745, 140-796, and 140-745 of SEQ ID NO: 1.
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> 3. An isolated nucleic acid encoding a hek-L protein capable of binding hek and affecting the growth and differentiation of cells expressing hek, wherein said nucleic acid comprises a nucleotide sequence that is at least 90% identical to a sequence selected from nucleotides 28-630, 28-573, 94-630, and 94-573 of SEQ ID NO: 3.
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> 5. An isolated nucleic acid encoding a human hek-L protein capable of binding hek and affecting the growth and differentiation of cells expressing hek, wherein said hek-L comprises an amino acid sequence that is at least 90% identical to a sequence selected from amino acids 1-202 and 1-219 of SEQ ID NO: 2 and amino acids 1-160 and 1-179 of SEQ ID NO: 4.
>
> 7. An isolated nucleic acid encoding a fusion protein comprising a hek-L polypeptide that binds hek and affecting the growth and differentiation of cells expressing hek, and an Fc polypeptide, wherein said hek-L comprises an amino acid sequence that is at least 90% identical to a sequence selected from amino acids 1-202 of SEQ ID NO: 2 and amino acids 1-160 of SEQ ID NO: 4.

Claims 8, 9, 10, and 11 depend from claims 1, 3, 5, and 7, respectively.

Contrary to the Examiner's contention, the claimed nucleic acids are not described solely "by the binding function of the protein" they encode. Rather, the claimed nucleic acids are at lest 90% identical to specific nucleotide sequences (claims 1 and 3) or the claimed nucleic acids encode amino acid sequences that are at least 90% identical to specific amino acid sequences (claims 5 and 7). In addition, the claimed nucleic acids encode proteins that are capable of binding hek and that affecting the growth and differentiation of cells expressing hek . Thus, applicants assert that the

claimed nucleic acids are adequately described by both structure and function. *See* Action at page 3.

Applicants respectfully request reconsideration and withdrawal of the rejection of claims 1, 3, 5, and 7-15 for lack of written description.

The Examiner rejected claims 1, 3, 5, and 7-15 under 35 U.S.C. § 112, first paragraph, as allegedly not being enabled for "an isolated DNA encoding a hek-L protein, said DNA comprising a nucleotide sequence that is at least 80% identical to a sequence set forth in SEQ ID NO:1 or 3." Action at page 3. Specifically, the Examiner alleged that "[t]he issue here is the breadth of the claims in light of the predictability of the art as determined by the number of working examples, the skill level of the artisan and the guidance presented in the instant specification and the prior art of record." Action at page 4.

Applicants respectfully traverse. Solely to expedite prosecution and without acquiescing to the rejection, applicants propose to amend claims 1, 3, 5, and 7 as discussed above. Claims 8, 9, 10, and 11 depend from claims 1, 3, 5, and 7, respectively. Applicants assert that the level of skill in the art of protein biology was high at the time the application was filed. Accordingly, applicants assert that it was within the skill in the art at the time the application was filed to use standard molecular biology techniques to make an isolated nucleic acid that is at least 90% identical to a specific, defined nucleic acid sequence. Applicants also assert that it was within the skill in the art at the time the application was filed to use standard molecular biology techniques to make an isolated nucleic acid that encodes a protein that is 90% identical

to a specific, defined amino acid sequence. Applicants further assert that it was within the skill in the art at the time the application was filed to determine if a protein encoded by a nucleic acid binds hek using the assays known in the art and/or discussed in the specification, e.g., at Example 5. Finally, applicants assert that it was within the skill in the art to determine whether the protein encoded by a nucleic acid affects the growth and differentiation of cells expressing hek using assays known in the art.

The test for enablement is not whether experimentation is necessary, but whether that experimentation is *undue* in light of the level of skill in the art, which in this case, was high. As the Federal Circuit articulated in *Wands*, "[t]he test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine." *In re Wands*, 858 F.2d 731, 737, 8 U.S.P.Q.2d 1400, 1404 (Fed.Cir. 1988). In *Wands*, the court considered an application directed to monoclonal antibodies, and found that "[t]he nature of monoclonal antibody technology is that it involves screening hybridomas to determine which ones secrete antibody with desired characteristics." *Id.* at 740.

Applicants assert that protein biology (i.e., making and screening polypeptides) also involves routine screening in order to find the polypeptides with the desired activity. In fact, protein biology is arguably more predictable than screening hybridomas because each successive round of experiments may be directed according to the results of the previous experiments. For instance, at the time of filing, one skilled in the art would make a series of polypeptides and determine their activity. He would then take only the polypeptides that were active and further alter them in a subsequent round of experiments. Moreover, one skilled in the art could deliberately make conservative

alterations, and thus would have a reasonable expectation that the polypeptides and polypeptide fragments would retain activity. Finally, one skilled in the art could align SEQ ID NO: 2 or SEQ ID NO: 4 with other, similar polypeptides using standard methods in order to predict which amino acids are more amenable to mutation.

This is in contrast to screening a random array of hybridomas, in which one skilled in the art has no directive input. Yet the Federal Circuit has found such screening of hybridomas not to involve undue experimentation. Applicant therefore asserts that making and screening polypeptides for desired activity also does not involve undue experimentation.

The Examiner also alleged that "the standard . . . of mutating a subject protein and testing to see if it retains the desired biological activity (in this case, for the ability to bind hek) is a position that has been routinely dismissed by the courts, as shown by the decisions cited above." Action at page 4. The Examiner cited *In re Fisher*, 427 F.2d 833, 166 U.S.P.Q. 18 (CCPA 1970); *Amgen v. Chugai Pharmaceuticals Co. Ltd.*, 927 F.2d 1200, 13 U.S.P.Q.2d 1737 (Fed. Cir. 1990); and *In re Wands*, 858 F.2d 731, 8 U.S.P.Q.2d 1400 (Fed.Cir. 1988) as allegedly supporting that proposition.

Applicants respectfully traverse. The Federal Circuit held in *Wands* that "[e]nablement is not precluded by the necessity for some experimentation such as routine screening." 858 F.2d at 736-737. The focus of the enablement analysis, therefore, is not on whether the experimentation is of a particular type, such as protein or antibody screening, but whether the experimentation is *undue*. As discussed above, applicants assert that the level of skill in the art was high as of the earliest priority date of the application, August 20, 1993. Applicants note that the Federal Circuit's

discussion in *Wands* concerned an application with a priority date of September 19, 1980, nearly 13 years before the earliest priority date of the present application. Yet the Federal Circuit found making and screening hundreds of hybridomas not to involve undue experimentation even then. Thus, applicants assert that 13 years later, making and screening polypeptides also does not involve undue experimentation.

The Examiner also cited *Amgen v. Chugai Pharmaceuticals Co. Ltd.*, 927 F.2d 1200, 13 U.S.P.Q.2d 1737 (Fed. Cir. 1990), as allegedly supporting the contention that experimentation requiring screening does not meet the enablement requirement. However, the claim at issue in *Amgen* recited only functional activity and no specific level of identity and no specific structure. In contrast, independent claims 1 and 3 each recite an isolated nucleic acid that has a specific level of identify (90%) to a specific nucleic acid sequence. Similarly, claims 2 and 4 each recite an isolated nucleic acid that encodes a protein having a specific level of identify (90%) to a specific amino acid sequence. Thus, applicants assert that the present claims are readily distinguishable from the claim at issue in Amgen and that the analysis in *Amgen*, which relates to a claim that recites only function, is not applicable.

Finally, the Examiner cited *In re Fisher*, 427 F.2d 833, 166 U.S.P.Q. 18 (CCPA 1970), as allegedly supporting the contention that any experimentation requiring screening does not meet the enablement requirement. Applicants assert that Fisher in no way stands for the proposition that making and testing is not permitted under the enablement requirement. Rather, *Fisher* held that "the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art." 427 F.2d at 839 (emphasis added). As applicants

discussed above, the level of skill in the art of protein biology was high at the time the application was filed. Furthermore, *Wands*, which was decided 18 years after *Fisher*, supports applicants' assertion that the enablement requirement is not concerned with the *type* of experimentation, but only whether that experimentation is *undue*, taking into account the level of skill in the art.

The Examiner also alleged

> [t]o argue that one can make material embodiments of the invention and then test for those that work in the manner disclosed or that the instant claims only encompass the working embodiments is judicially unsound. Unless one has a reasonable expectation that any one material embodiment of the claimed invention would be more likely than not to function in the manner disclosed or the instant specification provides sufficient guidance to permit one to identify those embodiments which are more likely to work than not, without actually making and testing them, then the instant application does not support the breadth of the claims.

Action at pages 5 and 6. The Examiner cited *Genentech, Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 42 U.S.P.Q.2d 1001 (Fed. Cir. 1997); *In re Fisher*, 427 F.2d 833, 166 U.S.P.Q. 18 (CCPA 1970); *Amgen v. Chugai Pharmaceuticals Co. Ltd.*, 927 F.2d 1200, 13 U.S.P.Q.2d 1737 (Fed. Cir. 1990); and *In re Wands*, 858 F.2d 731, 8 U.S.P.Q.2d 1400 (Fed.Cir. 1988) as allegedly supporting that contention.

Applicants respectfully traverse. First, applicants note that *Genentech*, which cites *Fisher*, *Amgen*, and *Wands* favorably, as the Examiner correctly noted, adds little to applicants' discussion of *Fisher*, *Amgen*, and *Wands*, above. Rather, *Genentech* simply reiterates the holding in those cases, that "[t]o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *Genentech*, 108 F.3d at 1364. Applicants do not dispute that holding, but add to it the holding in *Wands*, in which the court elaborated on "undue experimentation," finding that "[t]he test is not merely

quantitative, since a considerable amount of experimentation is permissible, if it is merely routine." *Wands*, 858 F.2d at 737.

Second, contrary to the Examiner's contention, the enablement standard does not require that one skilled in the art be able to predict which embodiments more likely than not will have the claimed activity. Further, applicants assert that none of the cases cited by the Examiner stands for that proposition. Indeed, the notion that the enablement standard requires predictability has long been rejected by the courts. For Example, in *Application of Angstadt*, 537 F.2d 498, 190, U.S.P.Q. 214 (Cust. & Pat. App. 1976), the predecessor of the Federal Circuit reversed the Board of Appeals on exactly that issue. Noting that the art involved in *Angstadt* was unpredictable and that some of the catalysts disclosed in the specification would not work in the claimed invention, the court nonetheless held that to require an applicant to test every embodiment of the claimed invention to distinguish those embodiments that work from those that don't would not only be prohibitive, but would discourage invention. *Id.* at 502-503. Instead, the court held that it is sufficient for enablement that "[w]ithout undue experimentation or effort or expense the combinations which do not work will readily be discovered and, of course, nobody will use them and the claims do not cover them." *Id.* at 503. Similarly, as discussed above, making polypeptides and screening them for activity is routine experimentation in the art of protein biology.

Third, applicants find it particularly difficult to reconcile the Examiner's position with the holding in *Wands*. In that case, the Federal Circuit did not hold that predictability was required. Rather, the court found that monoclonal antibody claims were enabled even though it was impossible for one skilled in the art to predict which

hybridomas would produce the claimed antibodies. Nor could one skilled in the art provide any directive input that would increase the likelihood that any given hybridoma would produce the claimed antibodies. Applicants assert, as discussed above, that the presently claimed invention is arguably more predictable than the invention discussed in *Wands.* Furthermore, also as discussed above, the presently claimed invention is also more amenable to directive input. Thus, applicants assert that the claimed invention falls squarely within the holding in *Wands*, and is therefore enabled.

Applicants assert that the specification enables claims 1, 3, 5, and 7-11 for at least the reasons discussed above and respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, first paragraph.

Rejection Under 35 U.S.C. § 112, second paragraph

The Examiner rejected claims 1, 3 ,5 and 7-15 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. Action at page 6. Specifically, the Examiner alleged that claims 1, 3, 5, and 7 "are vague and indefinite because in line 2 the claims recite 'and affecting the growth and differentiation of cells expressing hek' because it is unclear if the cells increase or decrease the growth and differentiation of cells expressing hek." *Id.* Claims 8-15 ultimately depend from claims 1, 3, 5, and 7.

Applicants respectfully traverse. Applicants assert that the recitation "affecting the growth and differentiation of cells expressing hek" is not indefinite. As the Examiner acknowledged, one skilled in the art would understand that a protein that affects the growth and differentiation of cells expressing hek may increase or decrease the growth and differentiation of those cells. Thus, one skilled in the art would understand what is

encompassed by that language. The term "affecting" is not indefinite simply because it encompasses both increases and decreases in growth and differentiation. Applicants assert that for at least those reasons, claims 1, 3, 5 and 7-15 are definite.

Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, second paragraph.

Applicants respectfully assert that the present application is in condition for allowance and request that the Examiner issue a timely Notice of Allowance. If the Examiner does not consider the application to be allowable, the undersigned requests that, prior to taking action, the Examiner call her at (650) 849-6656 to set up an interview.

Please grant any extensions of time required to enter this Response and charge any additional required fees to Deposit Account No. 06-0916.

Respectfully submitted,

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Dated: December 21, 2004

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